

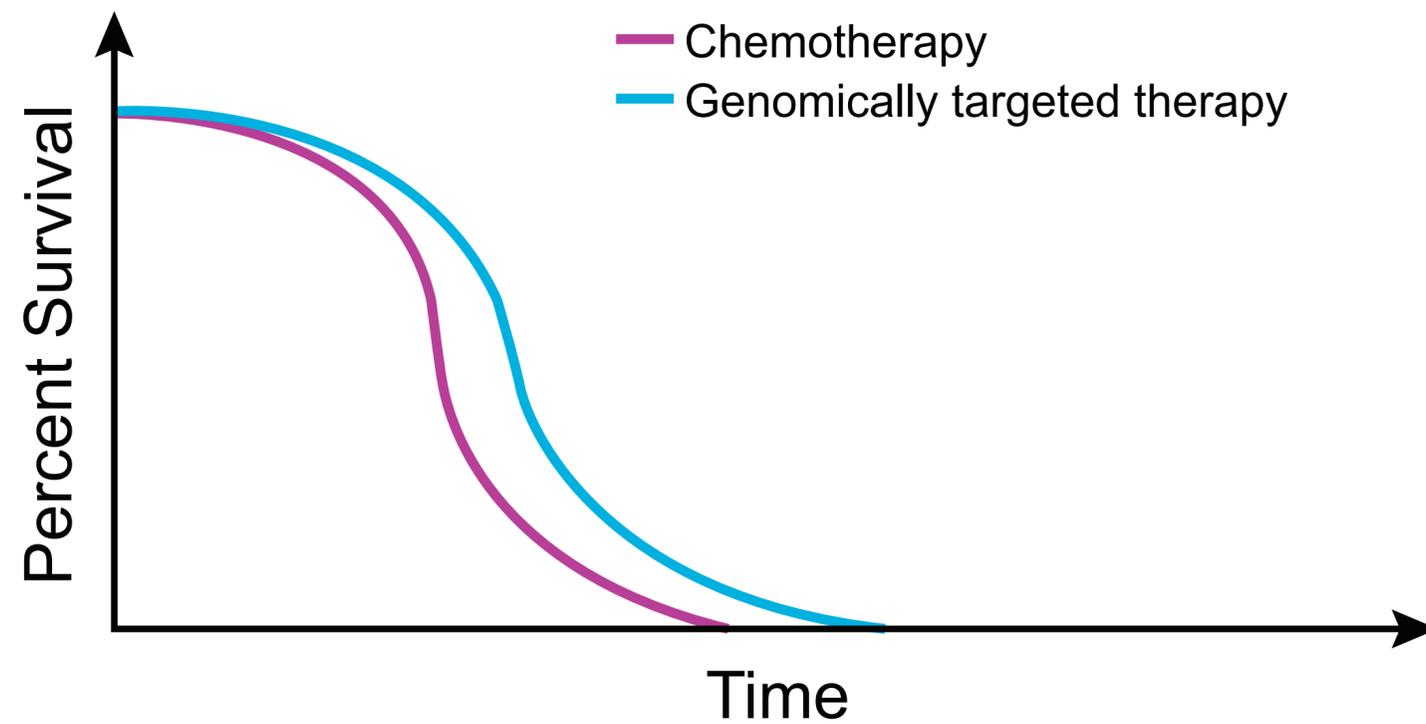
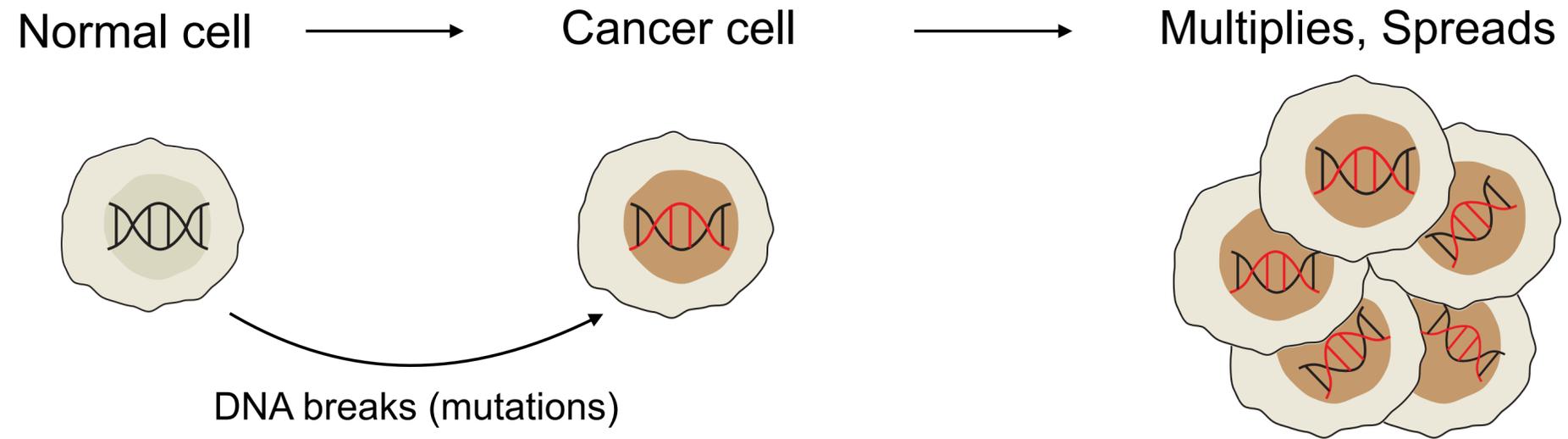


TUMOR IMMUNOLOGY GSK GRADUATE COURSE

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DIRECTOR, THE OLAYAN CENTER FOR CANCER VACCINES
IMMUNO-ONCOLOGY PROGRAM
DEPARTMENT OF SURGERY

Cancer

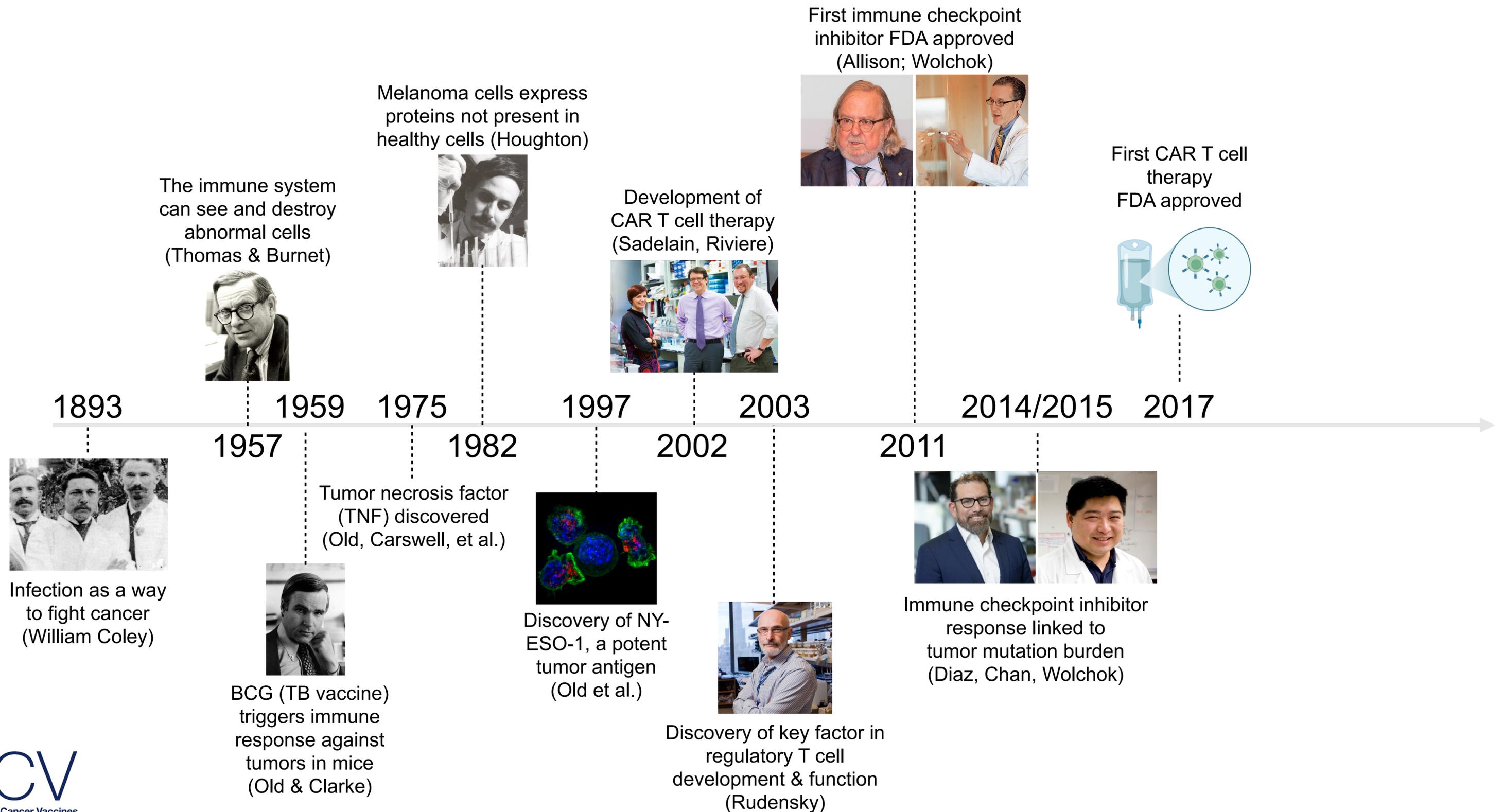


Is there an immune response to cancer?

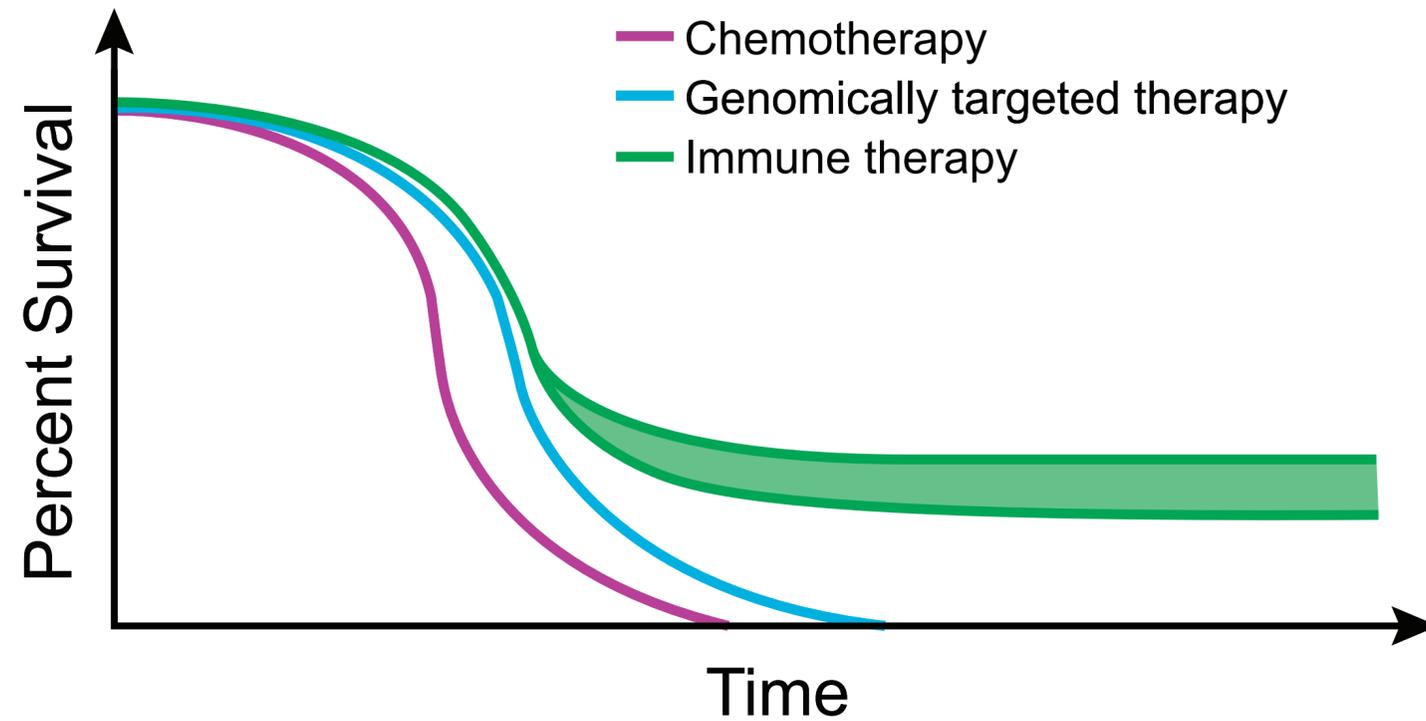
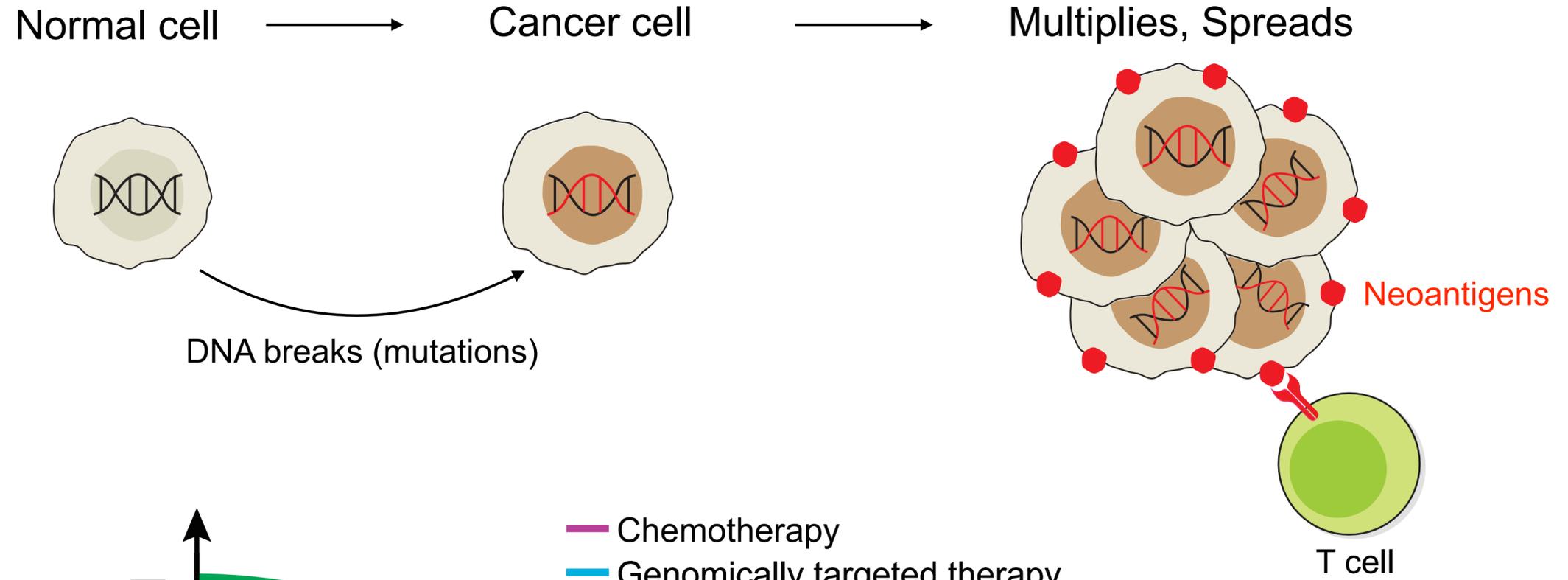
If cancer = self, how?

Can it be a therapy?

MSK's Legacy in Immuno-Oncology



Cancer

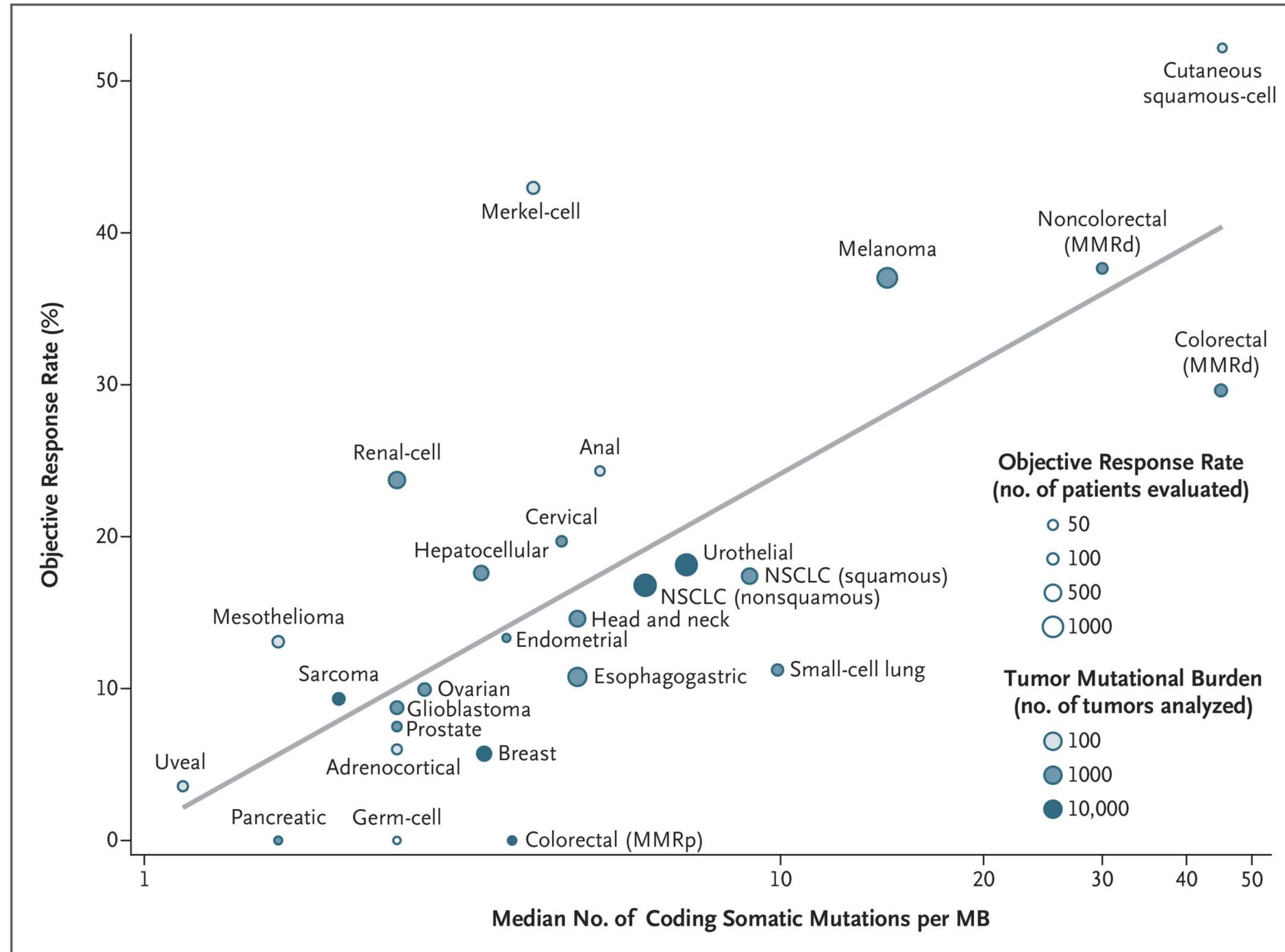


Immune Therapy
Living, adapting drug
“Lifelong” protection

Current immune therapies
- Effective in ~20% of cancer

What next?

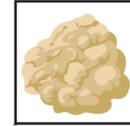
Few mutations = immunotherapy impossible?



Pancreatic Ductal Adenocarcinoma (PDAC)

Immunologically Invisible?

PDAC



Few neoantigens (~ 35/tumor)

Few T cells

~ 0% RR to checkpoint blockade



~ 80% of cancers



Cold

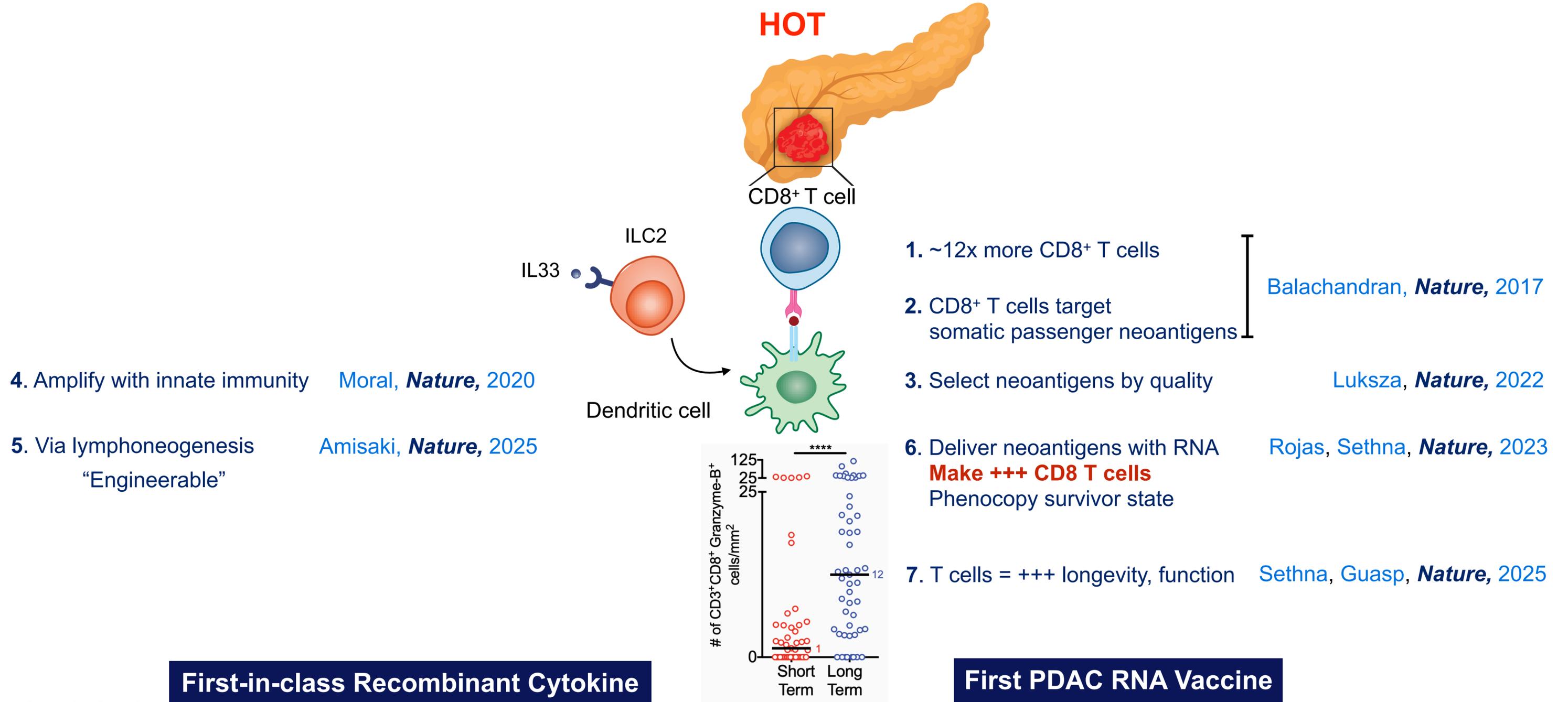
Immunotherapy
Insensitive

How do they do it?
How can we replicate it?

High unmet need: Second deadliest cancer, ~10% survival

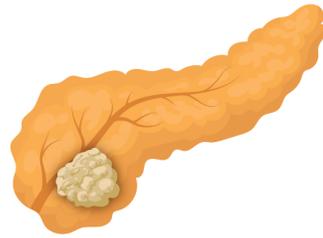
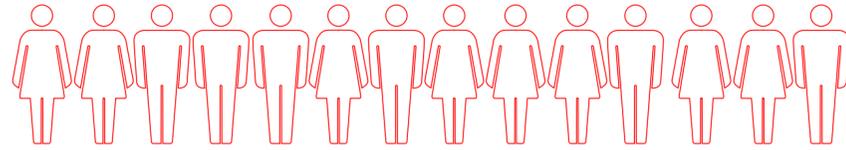
PDAC - Survivors to Solutions

Natural T cell Immunity

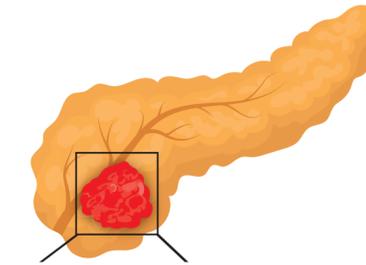


Is there Natural Immunity in Long-Term PDAC Survivors?

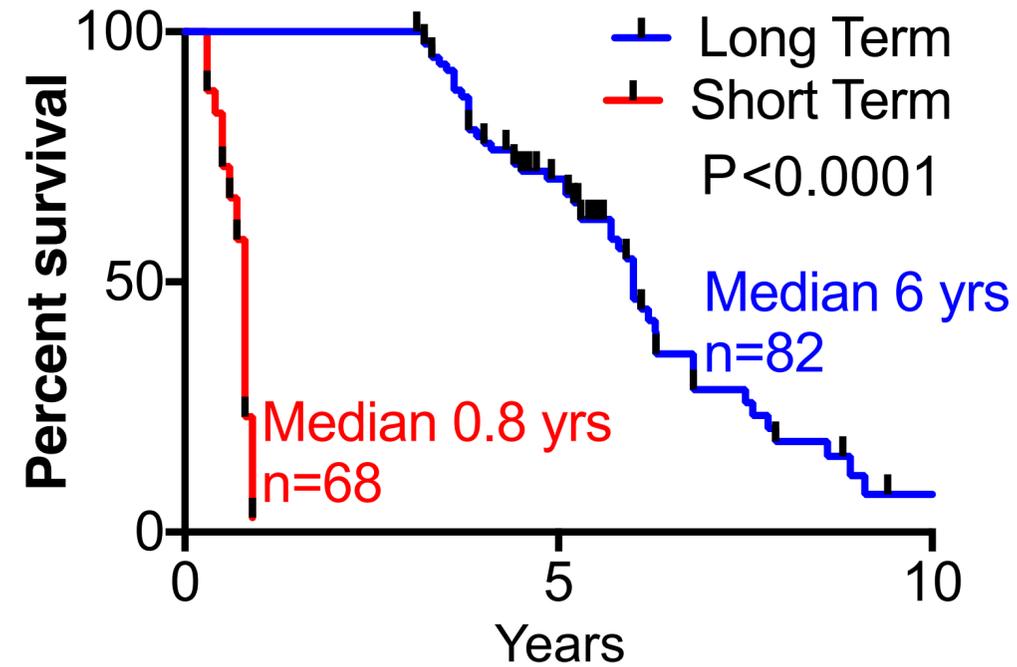
Short-term survivors (91%, < 5 years)



Long-term survivors (9%, > 5 years)



What is different?

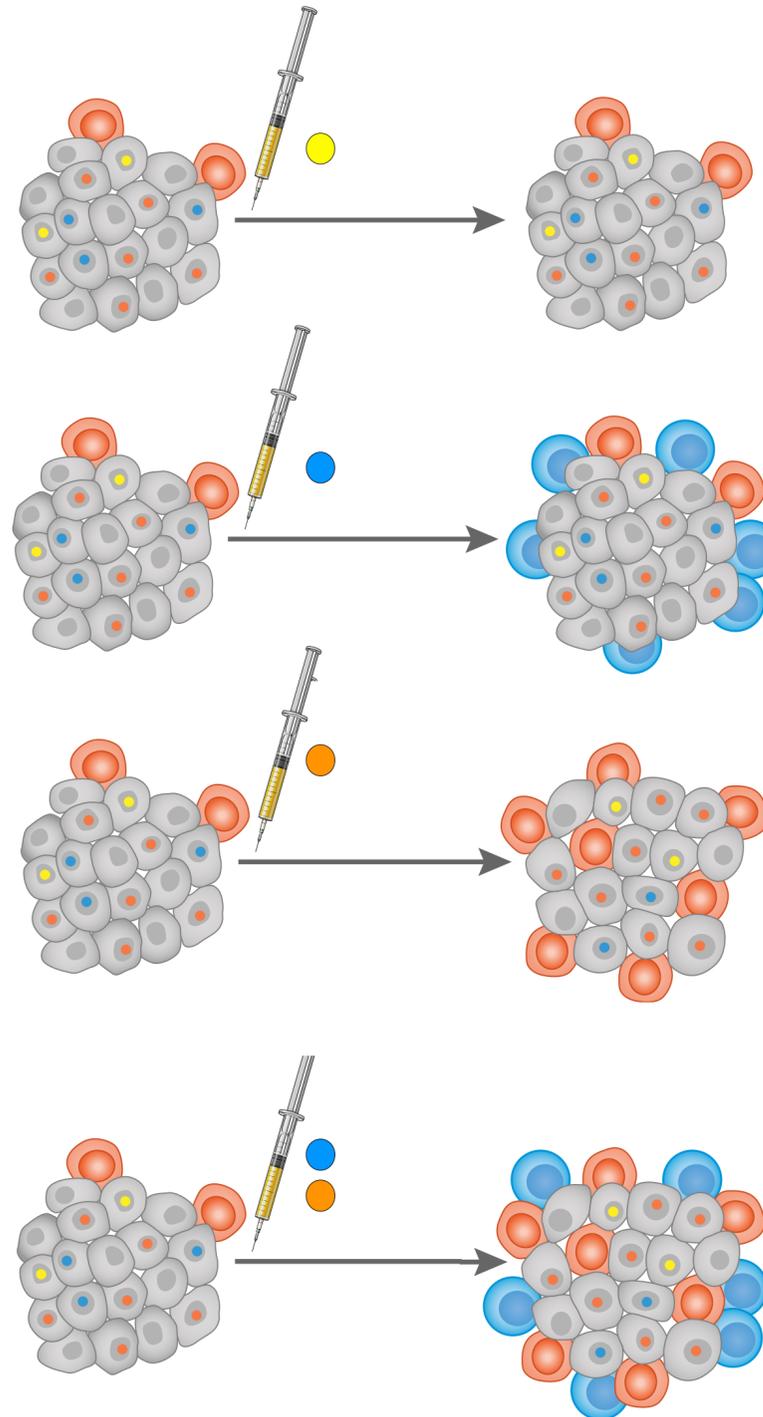


Neoantigens

Nonsynonymous Mutations

- ~ 10-30% bind MHC-I
- MHC-I: 75% SNVs, 25% indels
- Largely passenger
- **<10% are immunogenic**
- **Immunodominance**

- More immunogenic
- Less immunogenic
- Non immunogenic



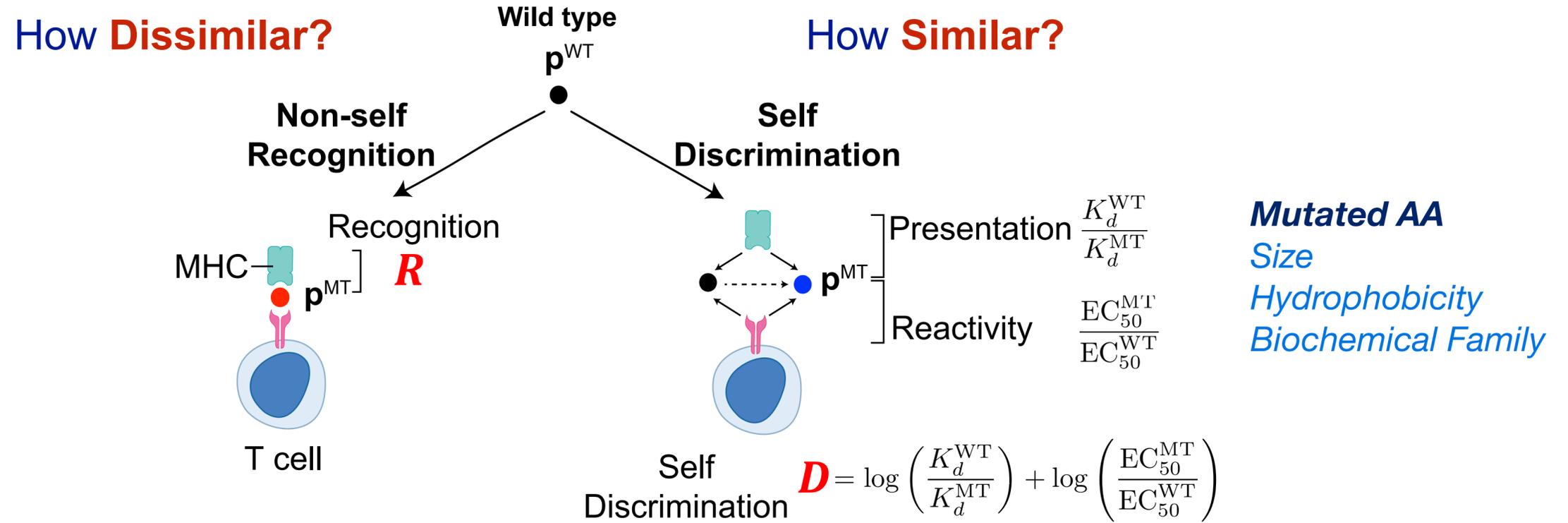
No response

Prime de novo

Amplify pre-existing

Prime de novo
Amplify pre-existing

The Neoantigen Quality Model



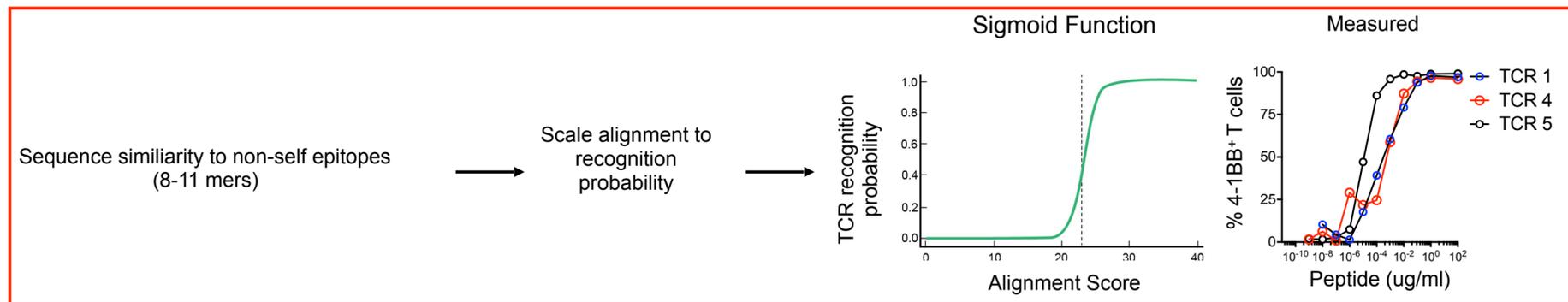
Neoantigen Quality $Q = R \times D$



Luksha

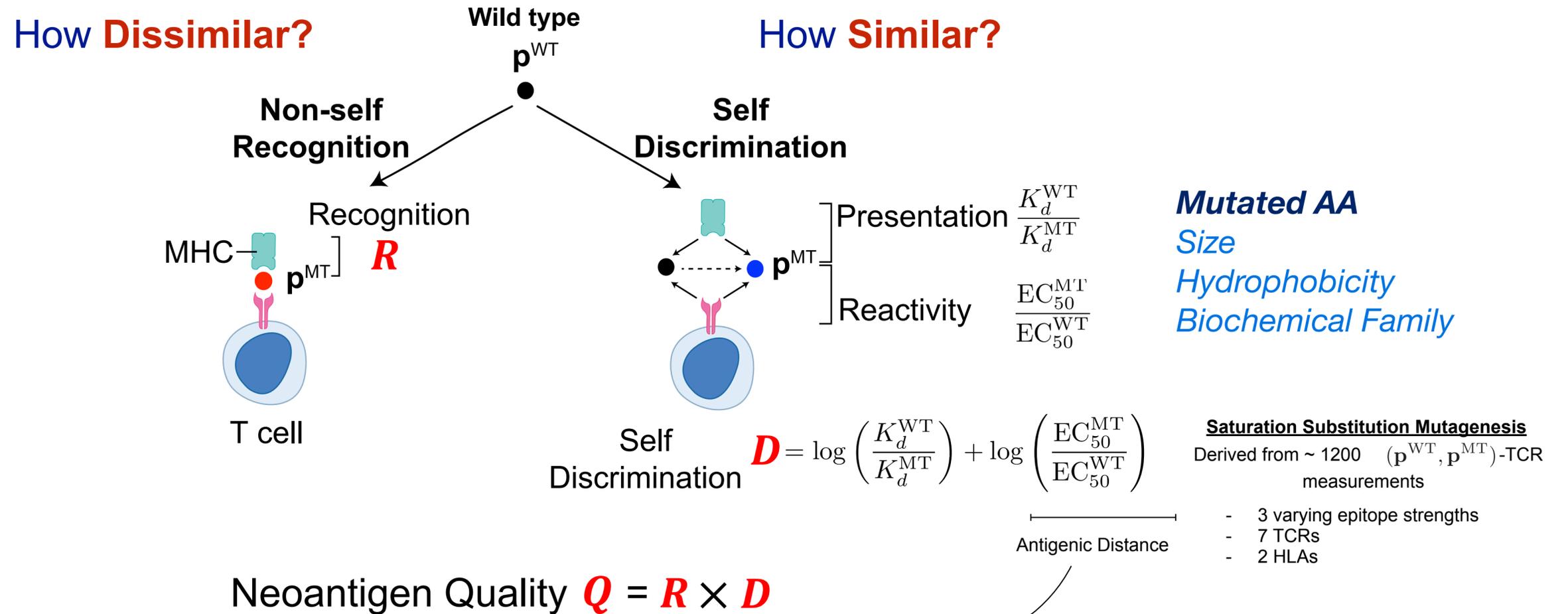


Greenbaum



Balachandran, *Nature*, 2017
 Luksha, *Nature*, 2017
 Luksha, *Nature*, 2022

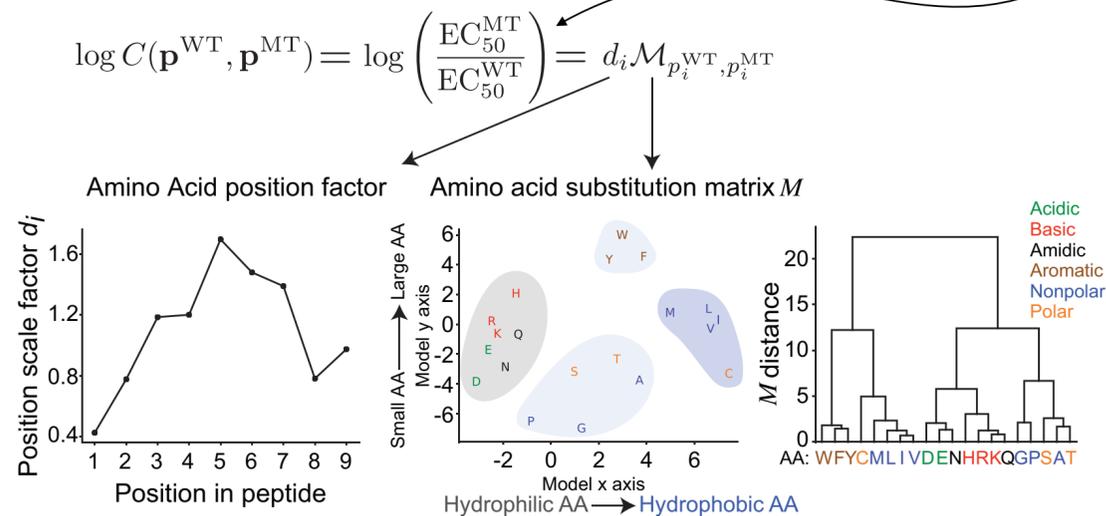
The Neoantigen Quality Model



Luksha

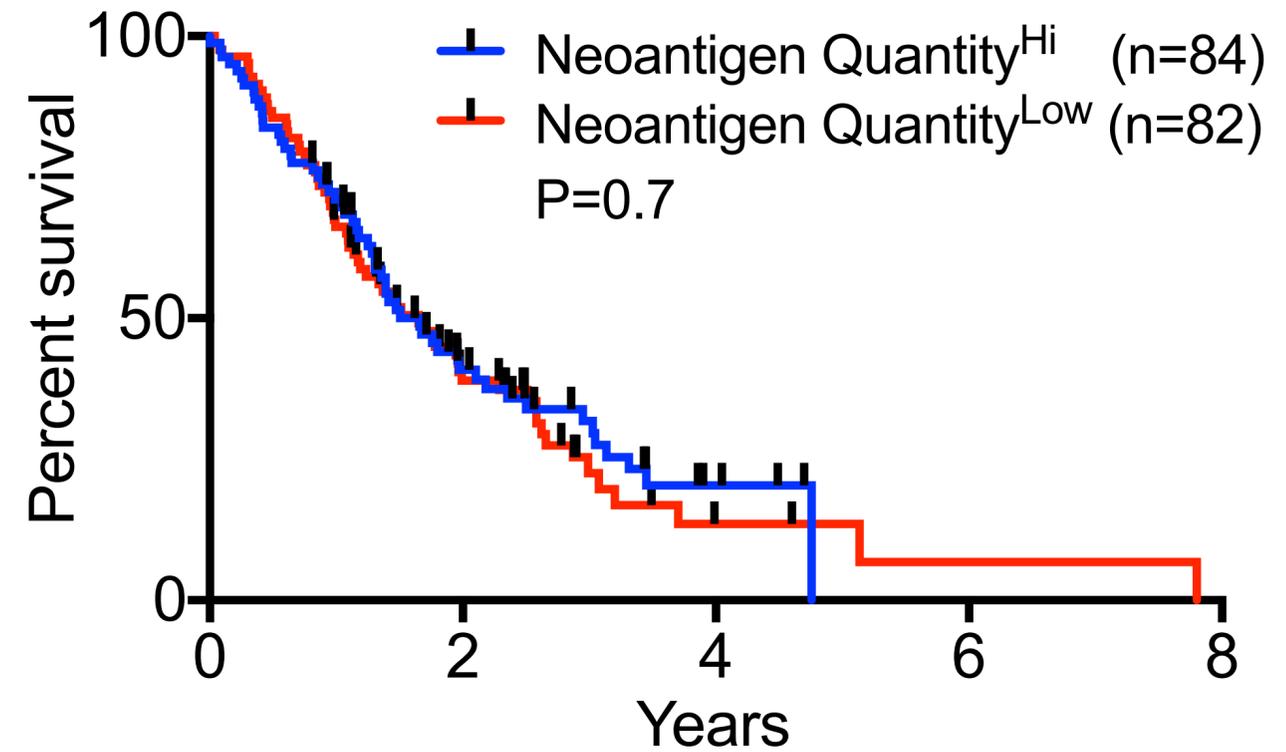
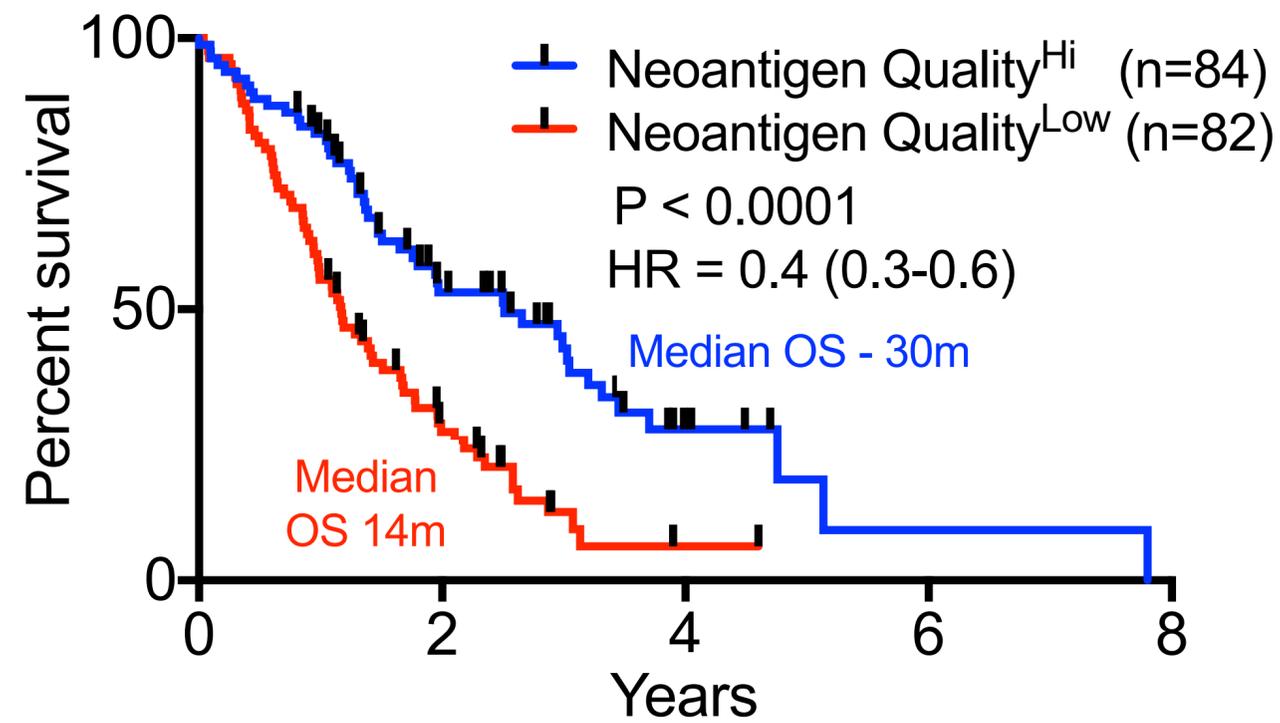


Greenbaum

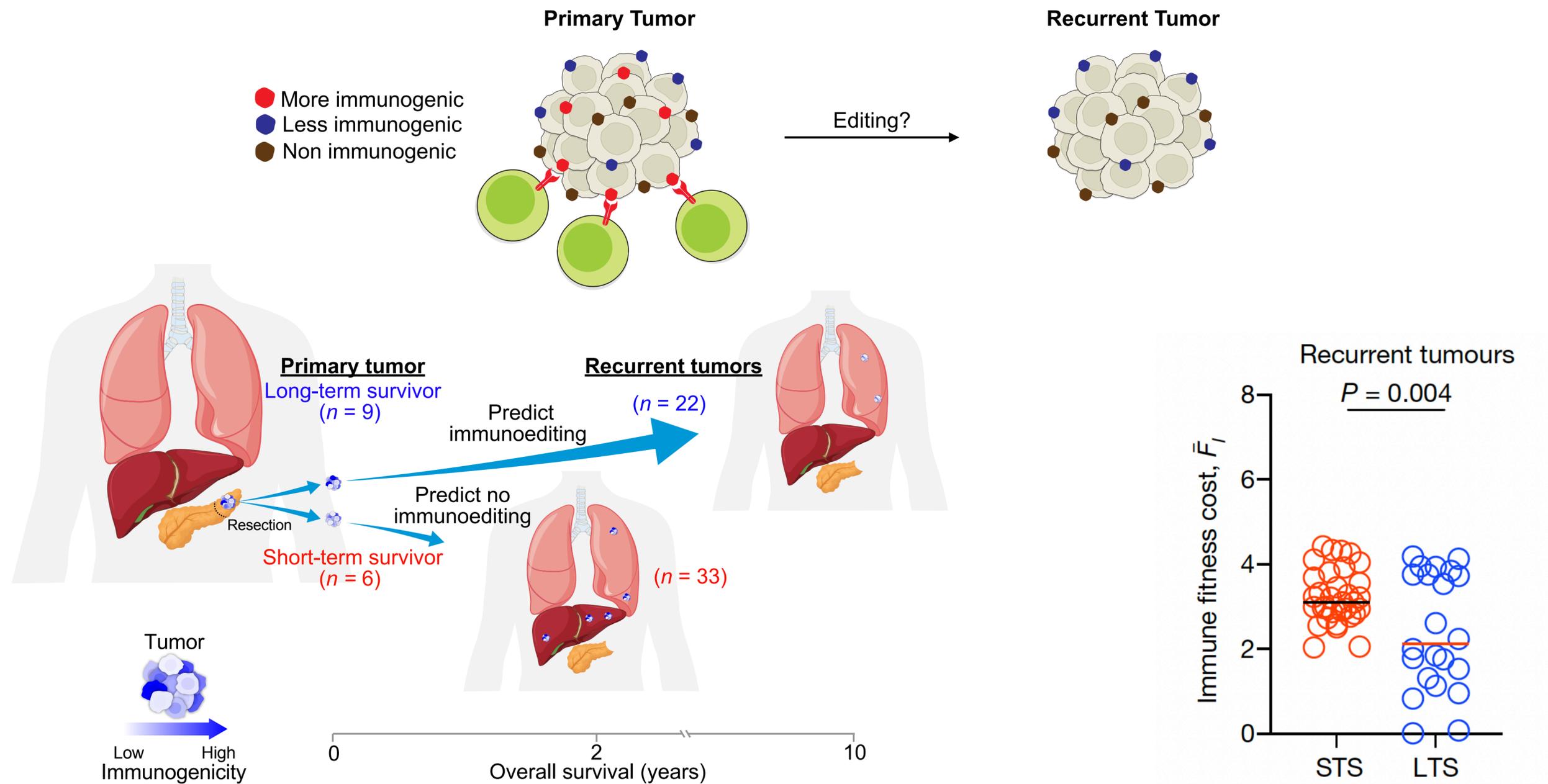


Neoantigen Quality not Quantity is Prognostic of Survival

PDAC



More Evidence of Natural Immunity in PDAC Survivors

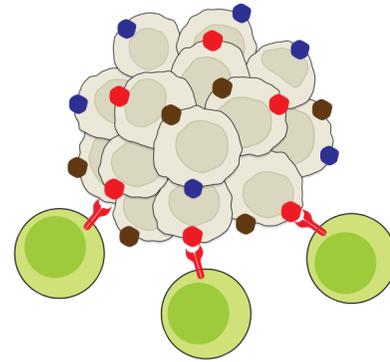


n = 70 longitudinal matched primary-recurrent tumors over 10 years

Can you phenocopy the survivor state?

Long Term Survivors

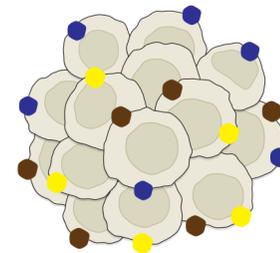
- Most immunogenic
- Mod immunogenic
- Less immunogenic



Natural Immunity

Unselected

- Mod immunogenic
- Less immunogenic
- Least immunogenic



Inducible Immunity?

To Phenocopy

Identify Neoantigens



Needs
Individualization

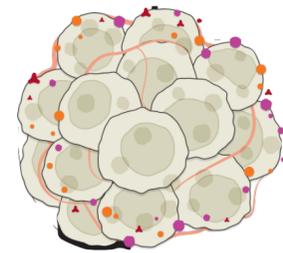
Deliver Neoantigens



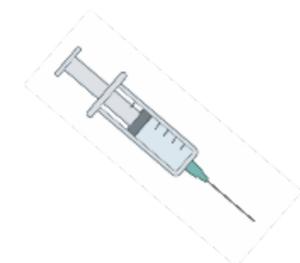
Cancer Vaccines: Next Promising Cancer Immunotherapy?

Strong, Specific, Functional, Durable T cells in Diseased Hosts

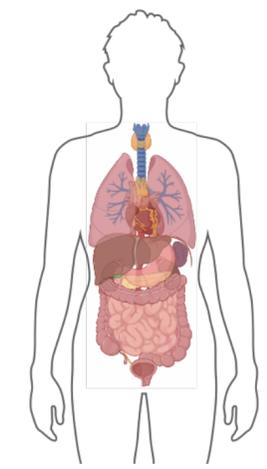
Antigen?



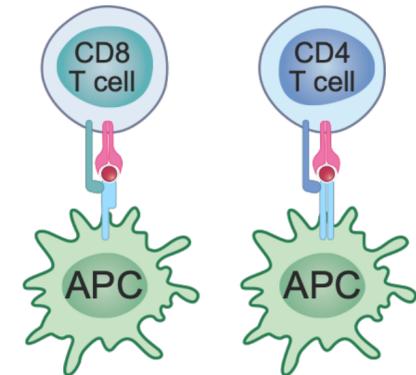
Delivery?



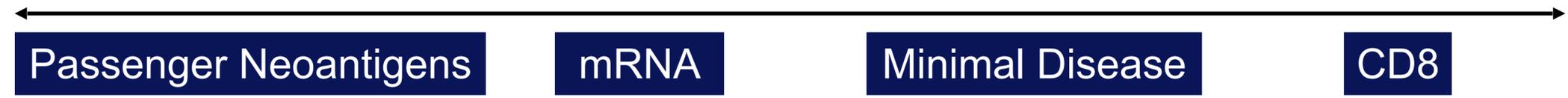
Host?



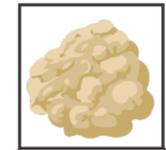
Cells?



REQUIREMENTS:



Ideal Combination



Pancreatic Cancer

Adjuvant RNA Neoantigen Vaccines

